1. INTRODUCTION

1.1 Complete project title	**DEXAMETHASONE FOR THE TREATMENT OF TRAUMATIC BRAIN INJURED PATIENTS WITH BRAIN CONTUSIONS AND PERICONTUSIONAL EDEMA: STUDY PROTOCOL FOR A PROSPECTIVE, RANDOMIZED AND TRIPLE BLIND TRIAL. (DEXCON TBI TRIAL)**
1.2 Trial registration	ClinicalTrials.gov number: NCT04303065 EUDRA number: 2019-004038-41
1.3 Protocol version	DEXCON-01-2019; Versión 1/October 2019 approved by the IRB: November 27, 2019

2. OBJECTIVES AND RATIONALE

2.1 Research questions	To estimate the efficacy of dexamethasone, with respect to placebo in patients with TBI and brain contusions and pericontusional edema. The primary outcome is the functional status (outcome) of TBI patients one and six months after the trauma according to the Glasgow Scale Outcome Extended (GOSE).
2.2 Background and rationale	Traumatic Brain Injury (TBI) is a global public health problem as there are more than 50 million cases of TBI per year worldwide. It constitutes one of the main causes of death and disability secondary to trauma and causes a great emotional and economic burden for the patients themselves, their families and the society. TBI is a complex and heterogeneous pathology, and this is one of the main reasons that could explain why the vast majority of clinical trials have failed in these patients. Among the drugs that have been tested in clinical trials in patients with TBI are glucocorticoids.

Based on the results of the MRC CRASH study, the current Clinical Practice Guidelines of the Brain Trauma Foundation do not recommend the administration of high doses of methylprednisolone to improve the prognosis for patients with TBI. However glucocorticoids, mainly dexamethasone, are still used in neurosurgical patients with various pathologies. For example, the benefit of dexamethasone in symptomatic patients with brain tumors and significant peritumoral edema, which is primarily vasogenic, has been well suggested. Cerebral edema is classified as cytotoxic and vasogenic. Cytotoxic edema is primarily intracellular and appears after ischemic insults. In vasogenic edema, however, water has an extracellular location and appears when there is a disruption or an abnormal increase in the permeability of the blood brain barrier.

TBI patients with brain contusions are a subgroup of TBI that can be clearly and practically defined on non-contrast head computed tomography (CT). They occur in approximately 35% of moderate-severe TBI cases. Contusion expansion, constituting progression of both hemorrhage and cerebral edema, occurs in approximately 50% of patients. Usually, the hemorrhage progression occurs most frequently within the first 12–24 hours, and the increase of the pericontusional edema occurs subsequently. Both increases can cause a rise of the intracranial pressure (ICP), leading to subsequent neurological deterioration. Currently there are no available therapies to prevent or treat this process.

Published studies have described the presence of a mixed component of cerebral edema (vasogenic and cytotoxic) in patients with TBI and cerebral contusions. Using diffusion tensor magnetic resonance imaging (DT-MRI), our group has shown that the radiological characteristics of the vasogenic edema in patients with brain tumors and cerebral contusions are similar.

For this reason, and taking into account the above mentioned preliminary results, the DEXCON-TBI trial was designed to assess the effect of dexamethasone in the clinical outcomes of TBI patients with brain contusions and pericontusional edema. In this study we tried to address TBI heterogeneity by limiting the enrolment to TBI patients with brain contusion and pericontusional edema. Our hypothesis was that dexamethasone can reduce the pericontusional edema and therefore improve clinical outcomes in this specific subtype of TBI patients.

3. ROLES AND RESPONSIBILITIES

3.1 Roles and responsibilities	**Trial steering committee (TSC)** Dr Jon Pérez Bárcena. Intensive Care Department. Son Espases Hospital. Palma de Mallorca. (Principal investigator) Dra Ana María Castaño León. Neurosurgery Department. 12 de Octubre Hospital. Madrid. Dr Alfonso Lagares Gómez-Abascal. Neurosurgery Department. 12 de Octubre Hospital. Madrid. Dr Jesús Barea Mendoza. Intensive Care Department. 12 de Octubre Hospital. Madrid. Dr Javier Ibánez Domínguez. Neurosurgery Department. Son Espases Hospital. Palma de Mallorca. Dr Guillem Frontera. Research Unit. Son Espases Hospital. Palma de Mallorca. **Statistician and Trial management:** Dr Guiem Frontera Unidad de Ensayos Clínicos. Hospital Universitario Son Espases. Instituto de Investigación de las Islas Baleares (IDISBA). Palma. Spain **Pharmacy Department:** Leonor Periañez Párraga Phamacy Department. Son Espases Hosptial. Palma de Mallorca

4. PARTICIPANTS, INTERVENTIONS AND OUTCOMES

4.1 Participants	Adults with TBI who fulfill the following inclusión criteria are eligible: -Patients who have suffered a head injury and have one or more cerebral contusions with visible pericontusional edema in the CT scan. -Patients with brain contusions in whom non-sugical treatment has been selected initially. -Age 18 or over and under 85

	-Signing of informed consent by the patient or by his legal representative. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use dexamethasone in a particular patient with TBI. This pragmatic approach will allow us to see whether the intervention improves patient outcomes under real-life conditions. The exclusion criteria are the following: -Patients with TBI and brain contusions who have required surgery to evacuate the cerebral contusion before randomization. -Patients with TBI who have required a craniotomy before randomization for any other reason: evacuation of subdural, epidural hematoma or depressed skull fracture. -Patients with an extracranial Injury Severity Score greater than 18 points. -Patients in whom the use of corticosteroids is contraindicated. -Patients who take oral corticosteroids chronically. -Patients included in another clinical trial. -Known intolerance or hypersensitivity to dexamethasone. -Patients with allergy or intolerance to the following excipients contained in dexamethasone / placebo capsules: lactose, corn starch or microcrystalline cellulose. -Patients with a history of psychotic disorders. -Patients with inability to take medication orally due to swallowing problems in which it is not indicated to place a nasogastric tube. -Pregnant or breastfeeding patients. -Patients in a GCS 3 points situation with bilateral dilated pupils. -Patients with associated spinal cord injuries. -Patient with any systemic condition that contraindicates the use of corticosteroids.
4.2 Interventions	Dexamethasone will be compared with matching placebo. Once it was verified that the patient met all the inclusion criteria and none of the exclusion criteria, a written informed consent will be obtained from the patients or from their legal representative if they lacked the capacity to provide consent. Then, a correlatively treatment kit will be assigned to the patient. Dexamethasone dosage will be a short and descending course: 4mg/6 hours (2 days); 4 mg/8 hours (2 days); 2 mg/6 hours (2 days); 2 mg/8 hours (2 days); 1 mg/8 hours (2 days); 1 mg/12

	hours (2 days). The patients in the placebo arm will receive the same amount of capsules. Dexamethasone (Fortecortin®) will be acquired from ERN, SA. Laboratories (Barcelona, Spain). The Son Espases Pharmacy Department will be in charge of developing and conditioning the 4mg, 2mg and 1mg dexamethasone / placebo capsules needed for 12 days of treatment, keeping the researchers blind. The preparation and conditioning of the capsules will be carried out following the standardized work procedures of the pharmaceutical laboratory and its quality controls, previously authorized by the Agencia Española del Medicamento (AEMPS). The Son Espases Pharmacy Department will be responsible for identifying the containers and sending them by courier to the participating hospitals. A record of the dispensing of test samples will be kept and will be sent in acknowledgment of receipt for control. Patients, clinical staff, evaluators of the results as well as the statistical team that will perform the analysis will not know the assigned treatment. A randomization list will be created for each hospital. The randomization sequence will only be known by the Pharmacy Department of Son Espases Hospital.
4.3 Outcomes	The primary outcome is the functional status (outcome) of TBI patients one and six months after the trauma according to the Glasgow Scale Outcome Extended (GOSE).The scale will be dichotomized in unfavorable outcome (GOSE 1-6) and favorable outcome (GOSE 7-8). Since the severity of the initial injury will significantly determine the final outcome of the patient, regardless of any treatment, the results of this study will be analyzed using the 'sliding dichotomy'. According to this analysis, patients with a less severe initial injury should have a better recovery than those with a severe initial injury. For example, a moderate disability in a patient for whom no more than death or severe disability could be expected is considered a good outcome, and vice versa, consider a moderate disability in a patient with excellent initial prognosis as poor outcome. Patients with a severe initial injury (GCS score of 4 to 5 or, or with a GCS motor score of 2 to 3) will be considered to have a favorable outcome if the 6-month GOS-E score is 3 or higher. Patients with a moderate-to-severe initial injury (GCS score of 6 to

	8 or, GCS motor score of 4 to 5) will be considered to have a favorable outcome if the 6-month GOS-E score is 5 or higher, and those with a less initial injury (GCS score of 9 to 12, GCS motor score of 6) will be considered to have a favorable outcome if the 6-month GOS-E score is 7 or higher. **Secondary outcomes** -Number of episodes of neurological deterioration in both groups of patients during the 12 days of treatment. -Symptoms associated with TBI in both groups of patients during the 12 days of treatment. -Volume of pericontusional edema before and after 12 days of treatment in both groups of patients. -Presence of adverse events between the two groups during the 12 days of treatment. -Neuropsychological tests between the two groups of patients one month and 6 months after the TBI.

5. TRIAL DESIGN

5.1 Description	The DEXCON TBI trial is a multicenter, pragmatic, randomized, triple-blind, placebo controlled trial to quantify the effects of the administration of dexamethasone on the outcome of TBI in TBI patients with brain contusions and pericontusional edema.
5.2 Trial diagram	**ELIGIBILITY CRITERIA:** Patients who have suffered a head injury and have one or more cerebral contusions with visible pericontusional edema in the CT scan. Age 18 or over and under 85 The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use dexamethasone in a particular patient with TBI. ↓

Signing of **INFORMED CONSENT** by the patient or by his legal representative.

RANDOMISE: dexamethasone or placebo

Give dexamethasone or placebo during 12 days

Complete outcome form at the end of the 12-days treatment.

Report adverse events during the treatment period.

Complete Extended Glasgow Outcome Scale

and Neuropsycologial test 1 month after the TBI

Complete Extended Glasgow Outcome Scale

and Neuropsycologial test 6 months after the TBI

6. SAMPLING AND RANDOM ASSIGNMENT

6.1 Sampling plan	Once it is verified that the patient meets all the inclusion criteria and none of the exclusion criteria, and after signing the informed consent by the patient himself or by the closest relative, the doctor responsible for the patient will correlatively assign the number to the patient.
6.2 Process for random allocation	To ensure a balanced sample size across groups over time, the statistician of the study will apply the block randomisation method with a block size of 2 (two possible sequences: AB and BA) and will be generated with the statistical package R, version 3.5.3, a list for each hospital. A limited number of treatments will be available in each hospital, sent from the Pharmacy Department of Son Espases Hospital, which will be numbered, and will be assigned in a correlative manner. Patients, clinical staff, evaluators of the results as well as the statistical team will be blinded to the assignment of medications. Only the pharmacist, who masks the capsules and labels the containers, will know the assignement of the codes, and will keep them blind until the last phase of the study, after the main statistical analysis, or when unmasking is required. Once it is verified that the patient meets all the inclusion criteria and none of the exclusion criteria, and after signing the informed consent by the patient himself or by the closest relative, the doctor responsible for the patient will correlatively assign the number to the patient.

7. STATISTICAL ANALYSIS

7.1 Intended comparisons	- Proportion of patients with good recovery (Glasgow Scale Outcome Extended 7 and 8) - Volume of pericontusional edema before and after 12 days of treatment in both groups of patients. - Presence of adverse events between the two groups during the 12 days of treatment. Adverse events of special interest included hyperglycemia, new-onset delirium and infections -Number of episodes of neurological deterioration in both groups of patients during the 12 days of treatment. - Symptoms associated with TBI in both groups of patients during the 12 days of treatment
7.2 Statistical methods used	The primary analysis will compare all patients allocated to dexamethasone versus those allocated to placebo, on an 'modifiend intention-to-treat' basis. A descriptive analysis of the baseline variables will be made for each treatment group, followed by a comparison between both groups. In the secondary analysis the effect of dexamethasone and placebo on the patient´s functional status will be compared with the GOSE at one month and at 6 months. The scale will be dichotomized in unfavorable outcome (GOSE 1-6) and favorable outcome (GOSE 7-8). Since the severity of the initial injury will significantly determine the final outcome of the patient, regardless of any treatment, the results of this study will be analyzed using the 'sliding dichotomy'. Between group differences will be calculated as the value of the dexamethasone group minus the value in the placebo grupo Values will be expressed as number of patients and percentage or median and first-third quartile (Q1-Q3) Unadjusted t-test (for continuous variables); chi-squared test (for binary variables); Mann-Whitney U test to compare median values will be used.

7.3 Additional analysis	We will conducta a pre-specified subgroup analyses in those patients with baseline pericontusional edema greater than 10 ml in the pre-inclusion CT scan

8. SAMPLE SIZE AND STATISTICAL POWER

8.1 Assumptions used for power calculations	In our previous studies we have described that among TBI patients with brain contusions not treated with dexamethasone, the proportion of patients with good recovery (GOSE 7 and 8) was 50%.
8.2 Sample size required or minimum detectable effect size(s)	Since the data available in this type of patients with this treatment is scarce and inconclusive, we will perform a randomized, triple-blind, placebo controlled trial with an interim futility analysis (interim analysis). The primary endpoint for the DEXCON TBI trial is the good recovery (GOSE 7-8) one month after the TBI. A study with 600 patients would have about 80% power (two sided alpha=5%) to detect a 12% absolute increased (from 50% to 62%) in good recovery (GOSE 7-8). It includes an inflation of 10% due to non-adherence (withdrawal of consent, loss to follow-up, cross-over or change of treatment).

9. DATA COLLECTION

9.1 Data sources	This trial will be coordinated from Son Espases Hospital. Data will be collected at each site by local investigators and sent to the TSC. These data will be collected from the patient's routine medical records and no special tests will be required. All data on adverse events, including those routinely collected as outcomes, will be collected and reported as recquired by the relevant authorities. Data will be collected by the investigator on the paper Case Report Forms (CRFs) and transmitted to the TSC through the Research

	Electronic Data Capture (REDCap). REDCap is a secure web application for building and managing online surveys and databases. Original paper CRFs will remain at each trial site. The data will be used in accordance with local law and ethics committee approval.
9.2 Assessment of data completeness	The trial procedures are based on routine clinical procedures and include (1) the oral administration of the trial drug using routine clinical use; (2) collecting routine clinical information from the medical records; and (3) informed consent. There are no complex procedures or interventions for the participants or investigators in this trial. Clinical management for underlying conditions will remain as per each hospital's standard protocol. Investigators/institutions are required to provide direct access to source data/documents for trial related monitoring, audits, ethics committee review and regulatory inspection. All trial-related and source documents must be kept for at least 5 years after the end of the trial.
9.3 Assessment of data quality	All completed questionnaires will be reviewed at the coordinating center by a clinically trained investigator who was unaware of the trial-group assignments.

10. ETHICS

10.1 Ethical concerns	Dexamethasone has a well documented safety profile. Nevertheless, data on adverse events, such as infectious complications, hyperglycemia or appearance of psychotic symptoms will be collected as secondary outcomes.
10.2 Consent or assent for participation in the trial	The GCS score is a method of assessing the level of consciousness in TBI patients. Patients with a GCS score of 15 are generally considered fully conscious, but those with a GCS score of 14 or less may not be fully conscious and would not be mentally capable of giving informed consent to participation in a clinical trial. Besides, a brain contusion is a clinical sign indicating significant brain injury, and patients with this diagnosis would not be physically or

	mentally capable of givin informed consent to participation in a clinical trial. Therefore, given that patients are eligible for inclusion in the DEXCON TBI trial if they have a TBI and have a brain contusion on a CT scan, in most cases they will, by default, be physically or mentally incapable of giving consent. If relatives are present, they will be provided with brief information about the trial. Specifically, the responsible doctor will explain to the relatives that the patient will receive the usual treatments for traumatic brain injury but that, in addition to these, the patient has been enrolled in a research study that aims to improve the treatment of patients with this condition. It will be explained that the study is being done to see whether using a drug called dexamethasone will help patients with head injury by reducing the amount of edema and inflammation into the brain, therefore preventing further brain damage. The relative will be informed that the patient will be given a treatment over 12 days of either dexamethasone or a dummy medicine (a capsule which does not contain dexamethasone). The doctor will explain that dexamethasone has been shown to improve outcome in patients with other types of brain injuries, such as tumors, and that, whilst we hope that it will also improve recovery after head injury, at present we cannot be sure about this. If requested, a brief information sheet will be provided. If relatives object to the inclusion of the patient in the trial, their views will be respected. If no relatives are present, the patient can not be included in the study.
10.3 Confidentiality	Data will be collected by the investigator on the paper Case Report Forms (CRFs) and transmitted to the TSC through the Research Electronic Data Capture (REDCap). REDCap is a secure web application for building and managing online surveys and databases. Original paper CRFs will remain at each trial site. The data will be used in accordance with local law and ethics committee approval.
10.4 Data protection	The data collected for the study will be identified with a code so that no information that could identify the patient is included, and only the study's research physician will be able to link the data to the patient and their medical history.
10.5 Declaration of	This trial is funded by the Sociedad Española de Medicina Intensiva

interest	y Unidades Coronarias (SEMICYUC) and the Fundación Mutua Madrileña. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

11. TIMELINE

Date	**Activity**
July 15; 2020	Study start
June 26; 2021	Fundación Mutua Madrileña 1-year grant
August 1; 2022	Interim analysis
June 27;2023	Fundación Mutua Madrileña 2-year grant
June 30; 2025	End of the Mutua Madrileña 2-year grant
June 30; 2025	End of recruitment